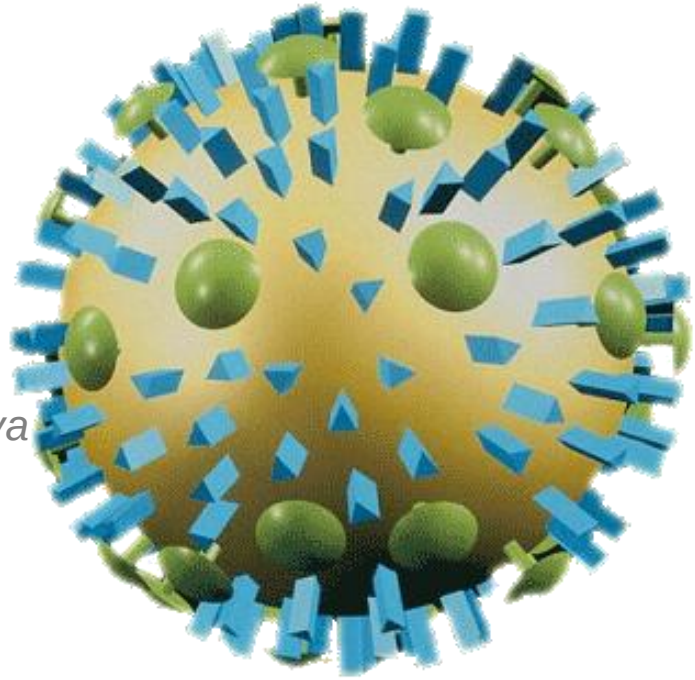
The Two Faces of Influenza

Annual, epidemic Influenza and

Pandemic Influenza

Sabine Arnoux March 2007, Eldoret, Kenya



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Often misunderstood and underestimated, Influenza is not just “a bad cold”!

Annual, winter influenza epidemics

Influenza pandemics: exceptional epidemiological events occurring every few decades

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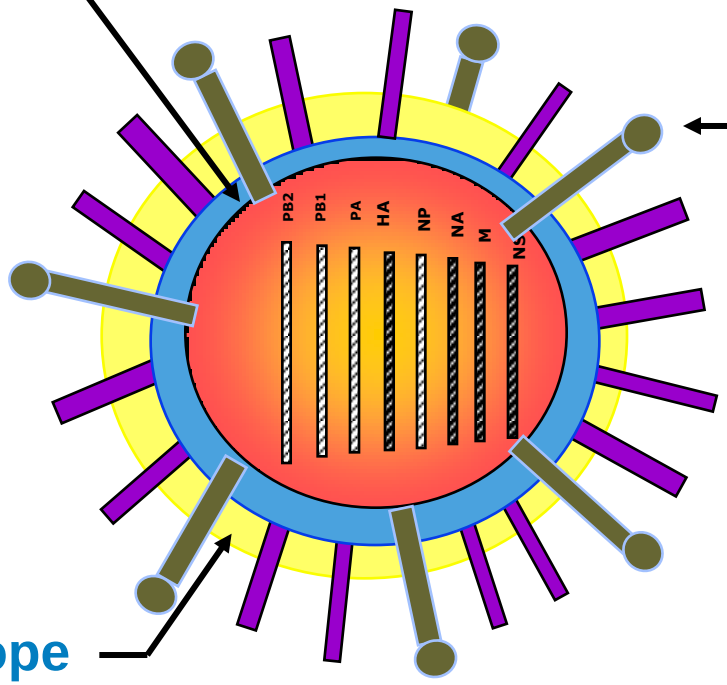
Influenza virion

Capsid (type A, type B, type C)



Envelope

Neuraminidase (NA)

Haemagglutinin (HA)

Surface antigens

Protective antibodies

Influenza virus mutations

Influenza type A viruses mutate frequently,
type B viruses mutate less frequently,

Mutation enables the virus to bypass the population's acquired immunity

Both the haemagglutinin and neuramidase surface antigens mutate

Mutation occur through two mechanisms

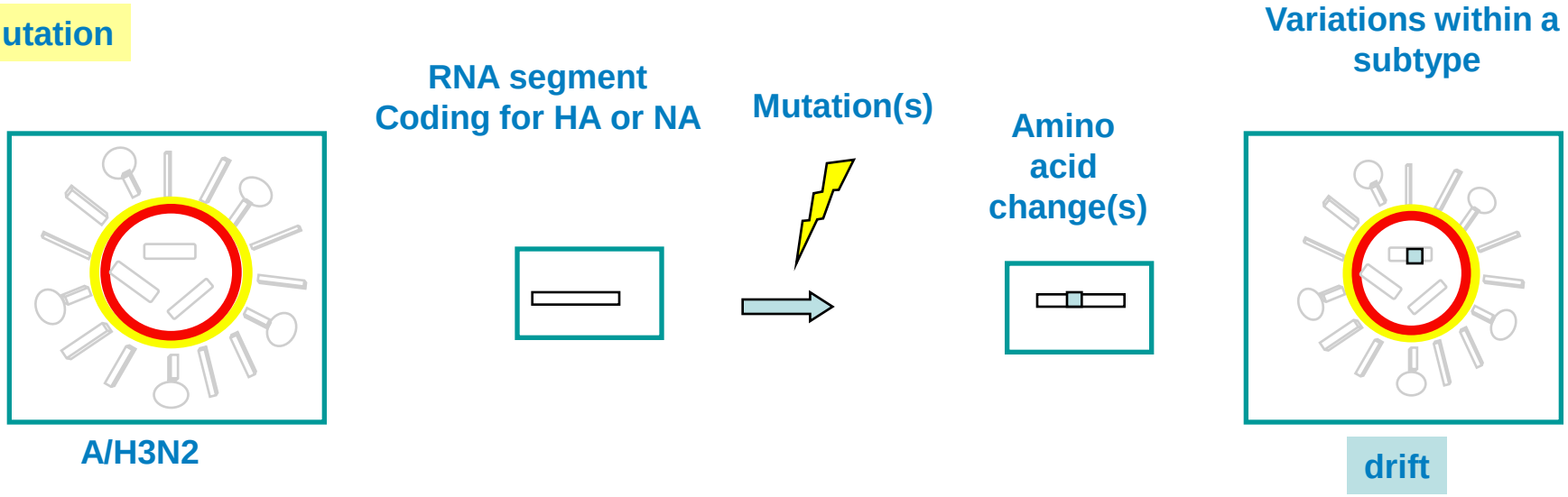
- **Antigenic drift**
  - Occurs continually
  - Leads to modified viruses that causes annual epidemics
- **Antigenic shift**
  - Occurs rarely
  - Leads to novel viruses that cause pandemics

Betts FR, Douglas RG, Mandell G.L., Douglas R. G., Bennett J.E., Principles and practice of infectious diseases, 3rd ed., 1990;39:1306-25

Antigenic drift

Minor variations in the Haemagglutinin and/or Neuramidase

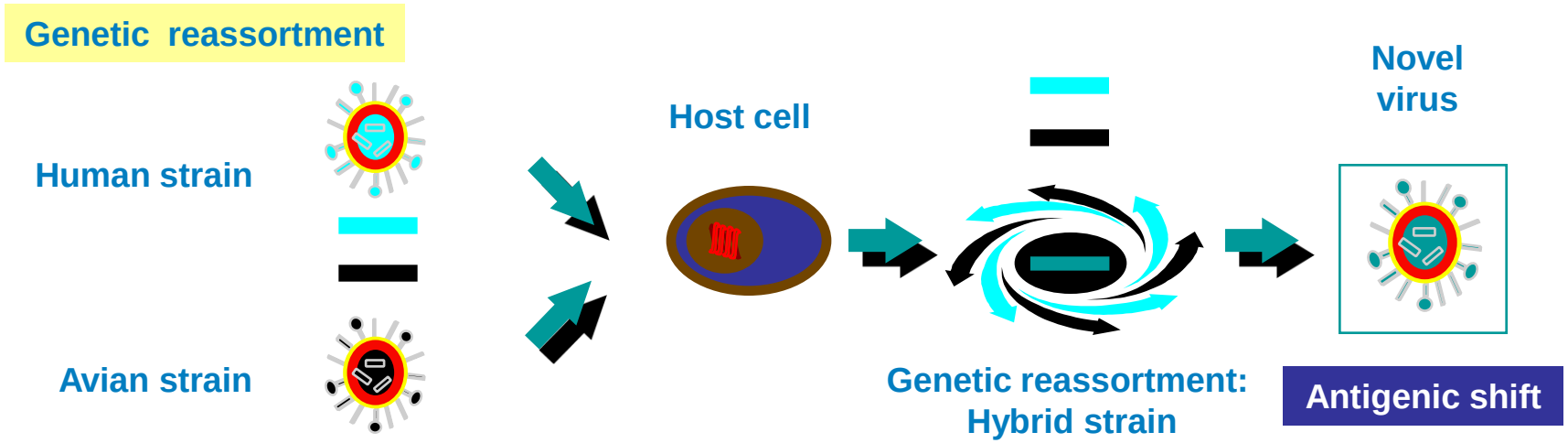
- Affects Influenza type A and B viruses
- Caused by mutations in the viral RNA
- Occurs each year within a subtype
- The resulting modified viruses cause annual <u>epidemics</u>



Antigenic shift

Emergence of a novel virus

- Only affects type A viruses
- Caused by major genetic modifications to the HA or NA
- The human population has little or no immune protection against the novel virus…
- …which leads to pandemics every 10 to 40 years



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Transmission

Virus is mainly spread through the air by coughing and sneezing, especially in closed public places: public transport, meeting rooms, ...

An infected person can transmit the virus to others from 1-2 days before flu symptoms start, and for 5 days afterwards

During each annual winter epidemic:

5 to 10 % of the world's population catches influenza

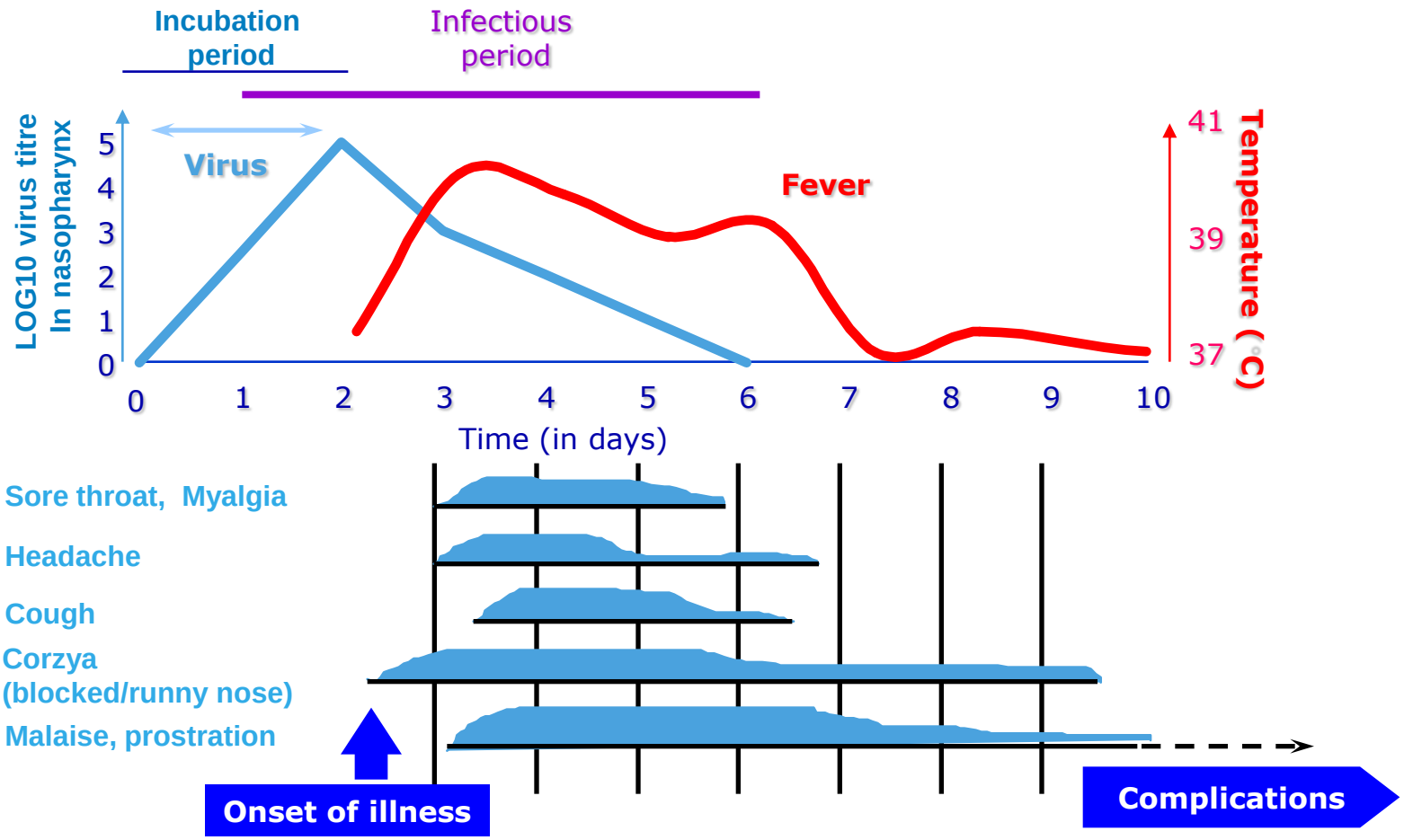
i.e., 500 million people

Including 3 to 5 million serious cases

100 000 to 1 000 000 deaths each year

Influenza does not discriminate:
it affects men and women, boys and girls of all ages, in all sectors of the population, and in all countries

Typical influenza illness



Complications

Mainly affect the elderly and infants

Infants

- Otitis, either viral or a secondary bacterial infection
- Exacerbation of chronic asthma
- More rarely: high fever and convulsions
- Myositis

Adults

- Bronchitis, sinusitis
- Fulminant viral pneumonia (seen during influenza pandemics)

Elderly persons and those with high-risk chronic medical conditions

- Acute bronchitis
- Pneumonia: viral or bacterial secondary infection
- Respiratory (asthma), cardiac, renal or metabolic (diabetes) decompensation

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Treanor JJ. Orthomyxoviridae: Influenza virus. In: Mandell GL, Bennette JE, Dolin R, editors. Principles and practice of infectious diseases. London: Churchill Livingstone, 2004: 1823-1849.

Influenza in at risk patients

Asthmatics

Diabetics

At risk patients

Influenza in asthmatic patients

1

Association of respiratory viral infections with asthmatic crisis in adults

138 adults with asthma

10/90 to 08/92, UK

> 40% of symptomatic asthmatic crisis were assiciated with viral respiratory infections

71% of the crisis were associated with cold symptoms

Influenza was associated with **severe crisis**

Nicholson et al., BMJ, 1993

Influenza is a severe disease for asthmatics

2

Does flu vaccination induce crisis in asthmatics?? →

12,000 patients 65-79 years old with asthma and COPD, 3 flu seasons

Asthma diagnosis as well as corticosteroid prescriptions **are the same** after vaccination and during low risk season

Asthmatic crisis **do not increase** significantly after vaccination

Tata et al., Thorax, 2003

Influenza vaccination does not induce asthma crisis in adults

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Flu vaccination prevents asthma crisis

1

349 asthmatic children

0-12 years

2 influenza seasons

Smits et al., Epidemiol Infect, 2002

All children

27% reduction in acute respiratory attacks

56% reduction during first influenza season

Children < 6 years

55% reduction in acute respiratory attacks

77% reduction during second influenza season

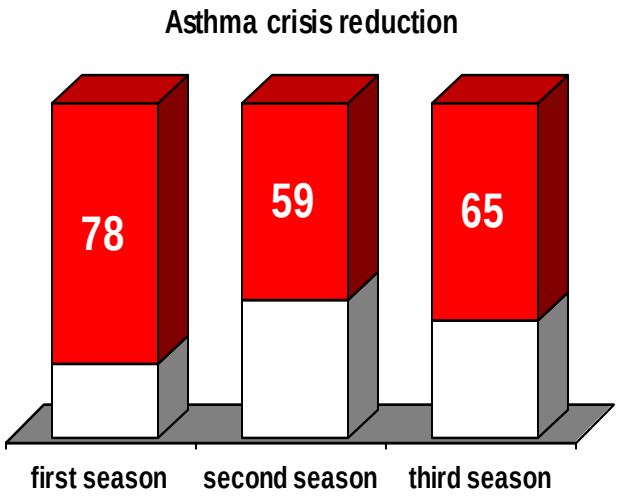
2

130.000 asthmatic children

1-6 years

3 seasons (USA)

Kramarz et al., J Pediatr, 2001



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Influenza risks in diabetics

Diabetics are

6 times more at risk to be hospitalized with an influenza diagnosis

3 times more at risk of dying of pneumonia or influenza

Mortality rate increases by **5 to 15%** during influenza epidemics

CFR for influenza: **12%**

Immune response

Response is satisfactory in **70% of patients**

Patients who don't respond to initial immunization respond to a second dose

Influenza consequences in diabetics are very severe

Immunization is very valuable in these patients

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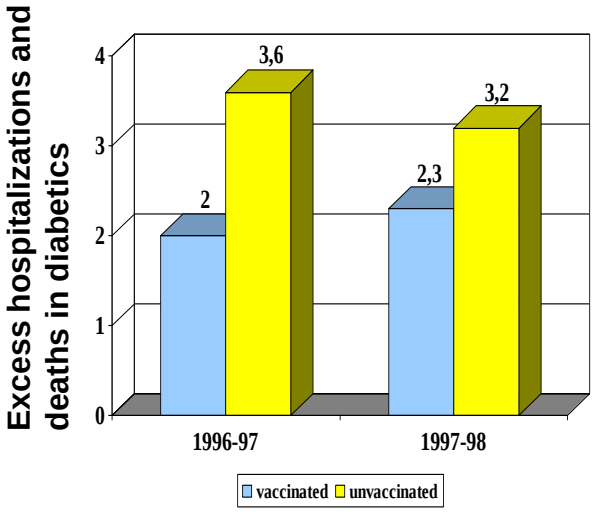
Effectiveness of influenza vaccination in diabetic patients



Effectiveness of influenza vaccination in the reduction of the risk of hospitalization for influenza or pneumonia, or death

50% in 1996-7

21% in 1997-8

In a case control study, influenza vaccination reduced hospitalization:

- **For pneumonia and influenza by 80%**
- **For bronchitis**
- **For diabetis without mention to any complication**
- **For diabetic comas**
- **For acidocetosis**

Influenza vaccination was EFFECTIVE since it reduced hospitalizations during influenza epidemics

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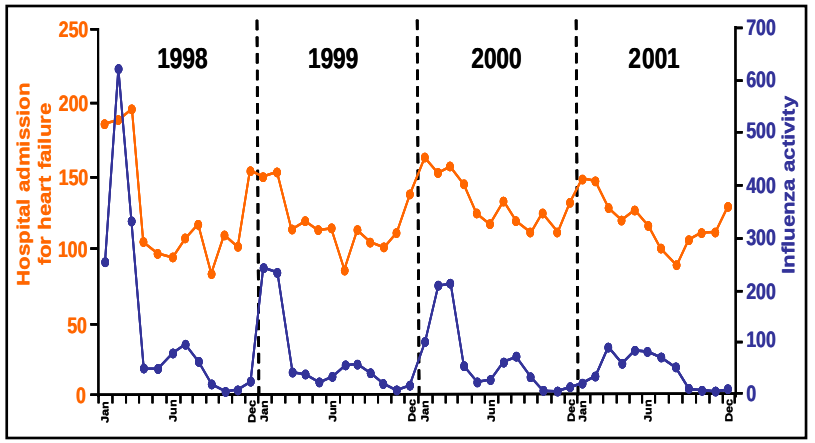
Influenza and cardiovascular diseases (CVD)

- **In 2002, CVD represented 29.2% (16.7 millions) of worldwide deaths**
- **Global CVD impact increases (increase in population age, urbanization)**

Flu activity and hospital admissions for heart failure In people older than 65 years, Hong Kong, 1998-2001



Obvious superposition between the flu activity peak and heart failure hospitalizations

Benefits of flu vaccination in patients with CVD

FLUVACS study (Argentina): flu vaccination and reduction of death and ischemic events in patients with Myocardial infarction

- Significant reduction in deaths (75%) and rehospitalizations
- Reduction of the triple risk (CV deaths, infarction and severe ischemia)
- Consistant results during 2 years, and with other studies

Four case control studies: reduction of:

- 49% for primary cardiac arrest risk
- 67% for the MI risk
- 55% for cerebral stroke (2 studies)

CONCLUSION: Flu vaccination is associated with a reduction in the risk of CV events

Groups at increased risk for Influenza-related complications

Influenza vaccination is the primary method for preventing influenza and its severe complications.
The Advisory Committee on Immunization Practices (ACIP) recommends annual influenza vaccination for the following groups:

Persons at high risk for influenza-related complications and severe disease, including

- **Children aged 6--59 months,**
- **Pregnant women,**
- **Persons aged ≥50 years,**
- **Persons of any age with certain chronic medical conditions; and**

Persons who live with or care for persons at high risk, including

- **Household contacts who have frequent contact with persons at high risk and who can transmit influenza to those persons at high risk and**
- **Health-care workers.**

(1). CDC. Prevention and control of influenza. Recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR July 29, 2006;54: RR8.

Influenza: vaccine, vaccine production

Influenza vaccines

Influenza vaccines first available in the 1940s

- **Whole virion vaccines: Connaught Laboratories (USA) in 1947 and Institut Mérieux (France) in 1968**

Today's vaccines

- **Trivalent**
  - 2 subtype A strains (H1N1, H3N2)
  - 1 type B strain
- **Two formulations per year: one for each hemisphere**
  - The WHO recommends the viral composition of each formulation, based on the predominant circulating strains
- **Different types of vaccines are available**
  - Inactivated, injectable (split virion, sub-unit and a few whole virion vaccines)
  - Live attenuated vaccine for nasal administration
- **Vaccine viral strains grown in embryonated chicken eggs**
  - Cell culture-based vaccines are in development

Influenza Vaccination:
The best defence against illness for more than 50 years

Effective

- **Vaccination mimics natural infection, providing protection for 6-12 months against the vaccine strains**
- **Protects 70–90% of vaccinated healthy adults**
- **Reduces complications and mortality by 70--85% in elderly persons**

Beneficial to society

- **Vaccination reduces the risk of transmitting the virus to others:**
  - Persons at risk of complications of influenza infection (the elderly, infants…)
  - Family, friends, colleagues…

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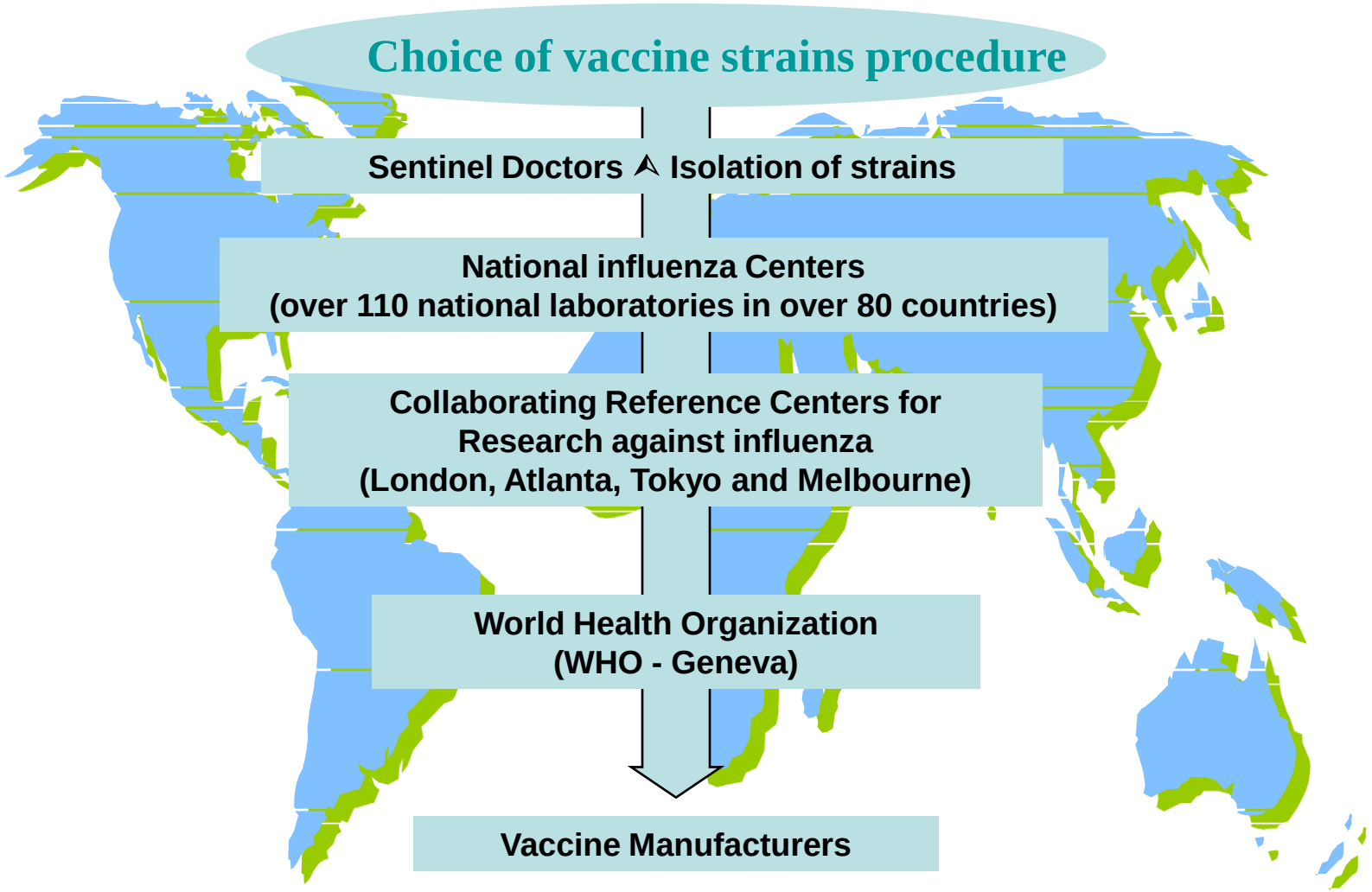
International surveillance network



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Hannoun C. Role of international networks for the surveillance of influenza. Eur Journal of Epidemiol 1994;10:459-61

Most countries in the world depend on European vaccines

- **Around 300 million doses produced yearly worldwide in 2004**
- **Influenza vaccine-producing countries:**
  - Europe (UK, France, Germany, Italy, Netherlands), Canada, USA, Japan, Australia
  - 12% of world population with 95% of global vaccine production
  - Production capacity of European countries: 190 million doses (65%)
- **International Area (outside US, Western Europe, Canada, Australia & Japan): 85 M doses**
  - 97% of these doses are produced in Europe

Current influenza immunization rates are very different around the world

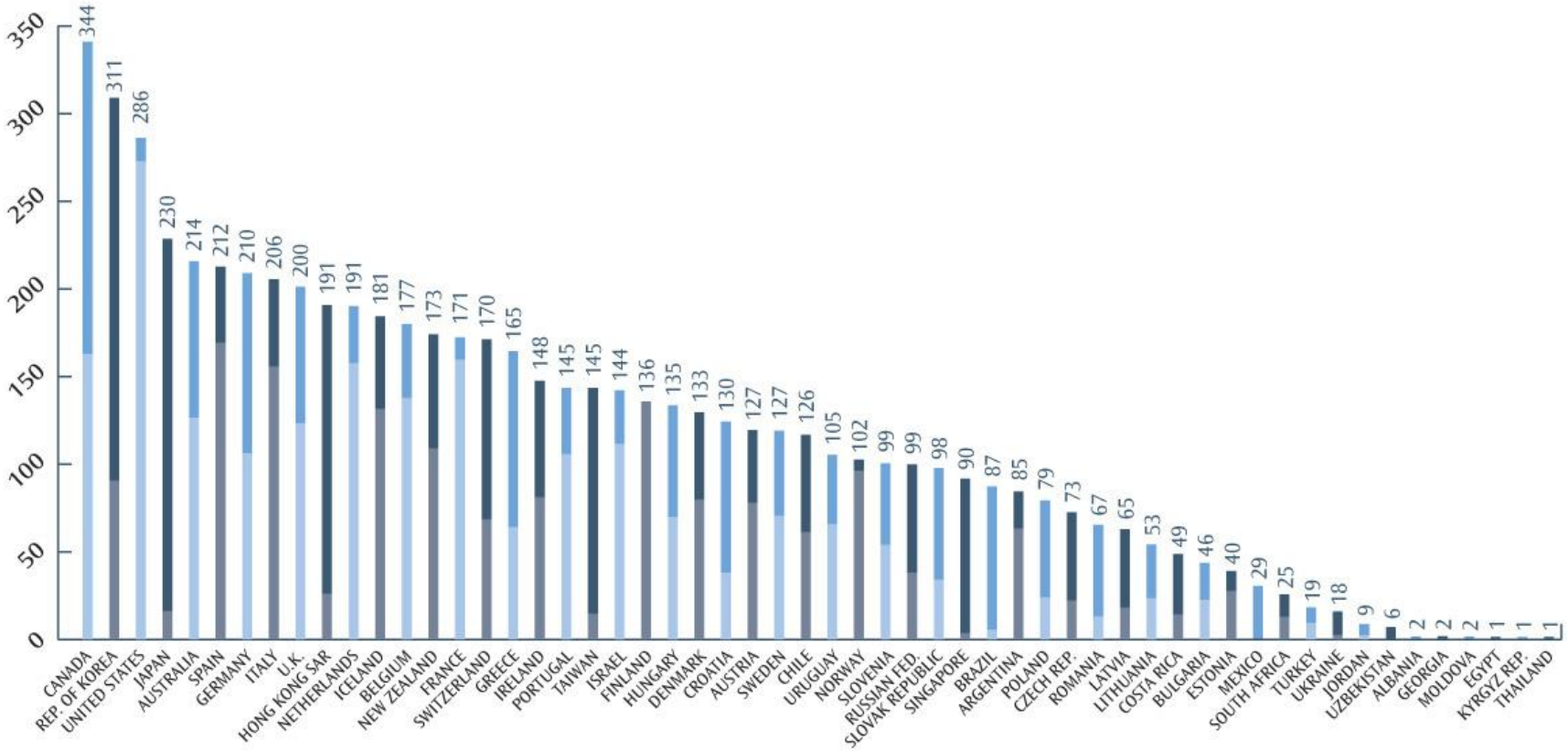

Fig. 3. Influenza vaccine distribution in 56 developed and rapidly developing countries in 2003 indicated by the number of doses of vaccine distributed in each country per 1000 total population (adapted from [17]).

(17) Fedson DS. The macroepidemiology of influenza vaccination in 56 countries, 1997-2003: a report from the macroepidemiology of influenza vaccination (MIV)
Study Group. Vaccine, 2005, In Press, Uncorrrected Proof.

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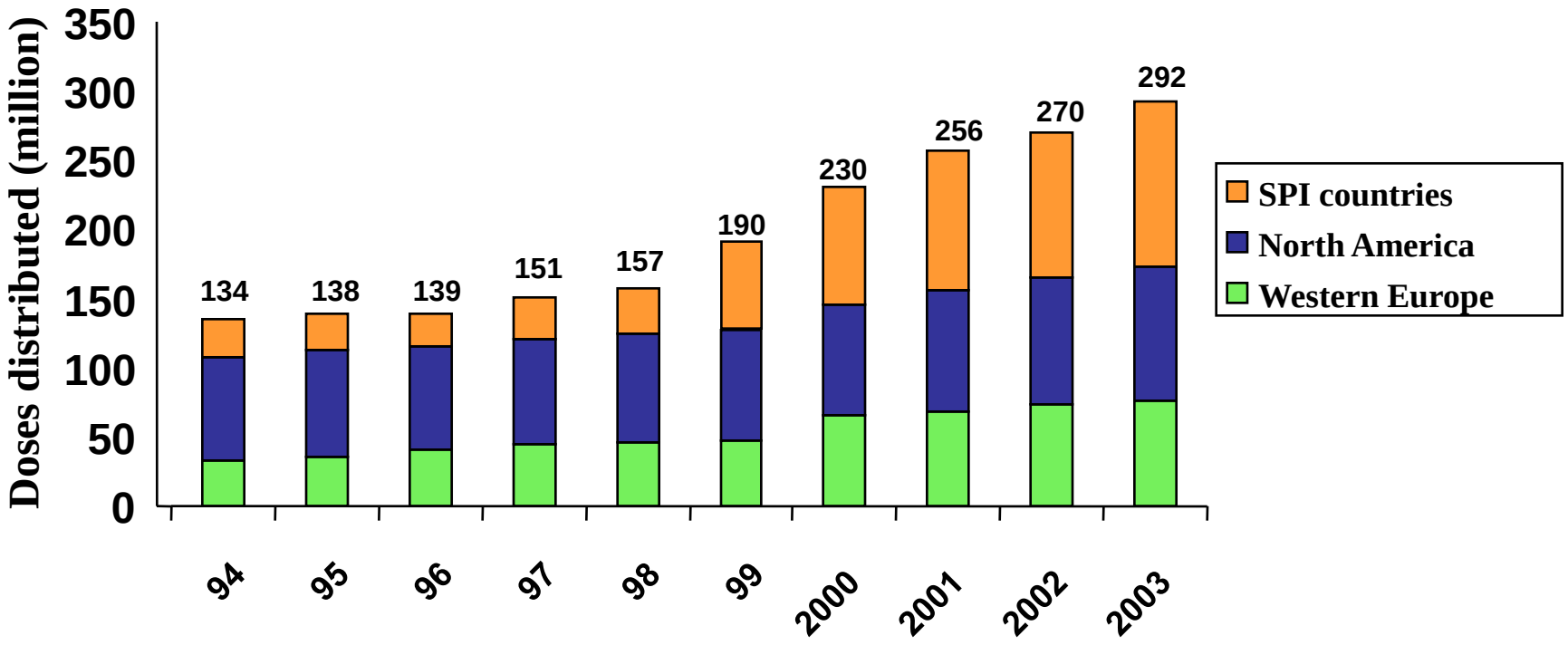
Inter-Pandemic Years: Global Influenza Vaccine Distribution 1994 – 2003

292 million doses vs > 6 billion world population



Source: International Influenza Vaccine Supply Task Force 2004

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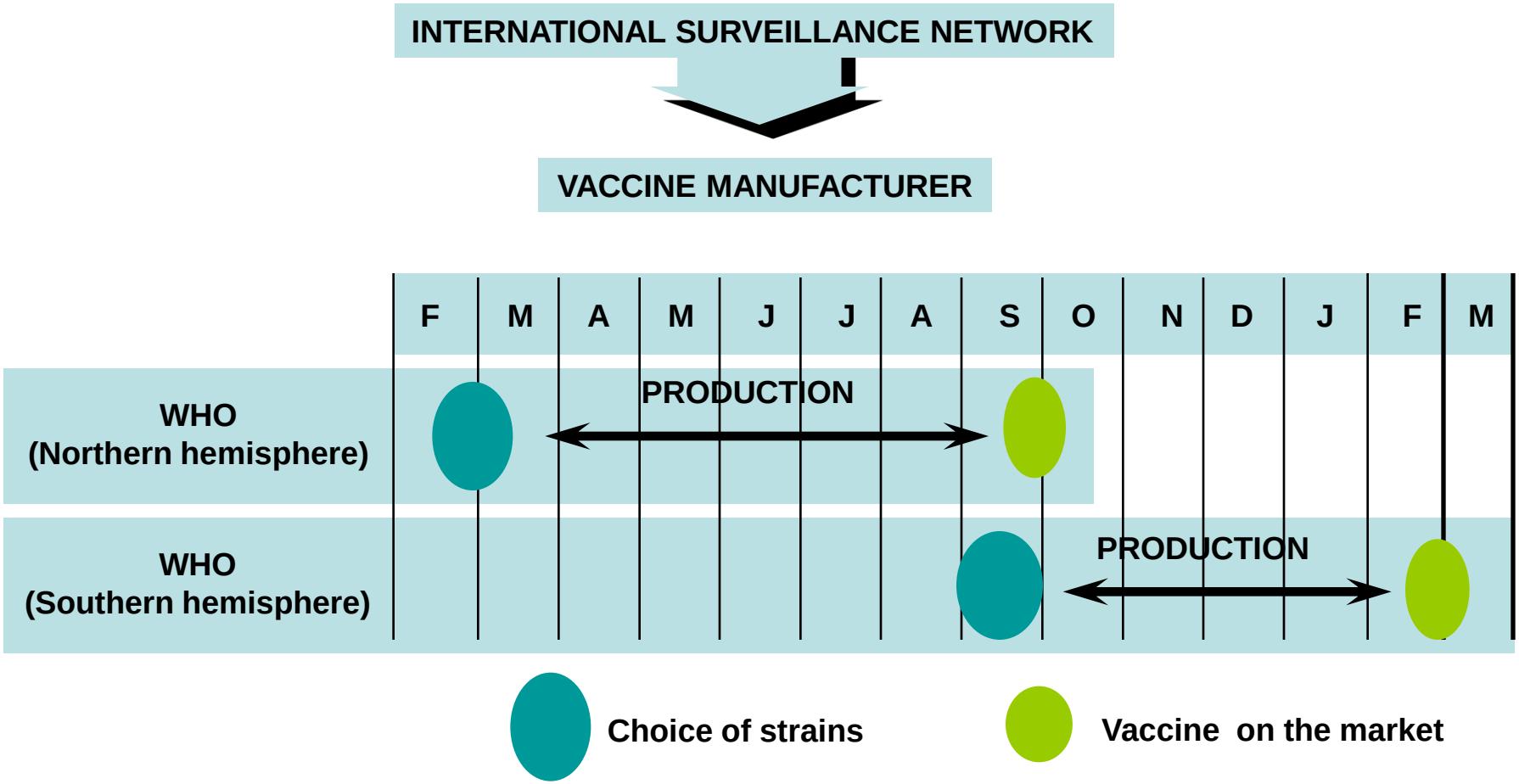
Influenza vaccine
Manufacturing time-table



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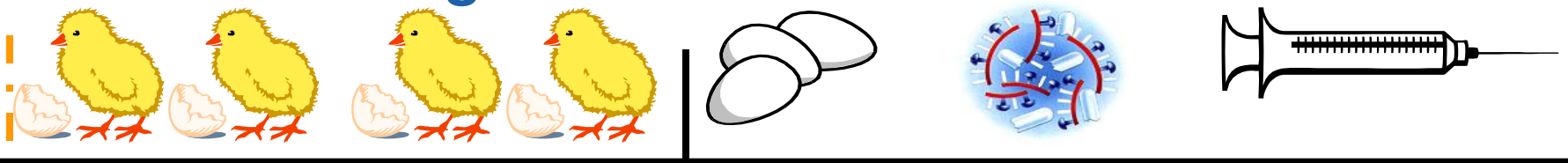
Aventis Pasteur

Influenza vaccines:

Manufacturing timetable



Egg supply organisation

Egg supply for production

Seed lots

Monovalent batches

Blending

Filling / Packaging

Packaging documentation

Pharmaceutical file

MA

Ref Member State Release

Clinical trial

Vaccine Delivery

D0 - 6 months

D0
WHO meeting
D0 = mid Feb

Reagent availability End of May

July/August

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The threat of Pandemics

What is pandemic influenza?

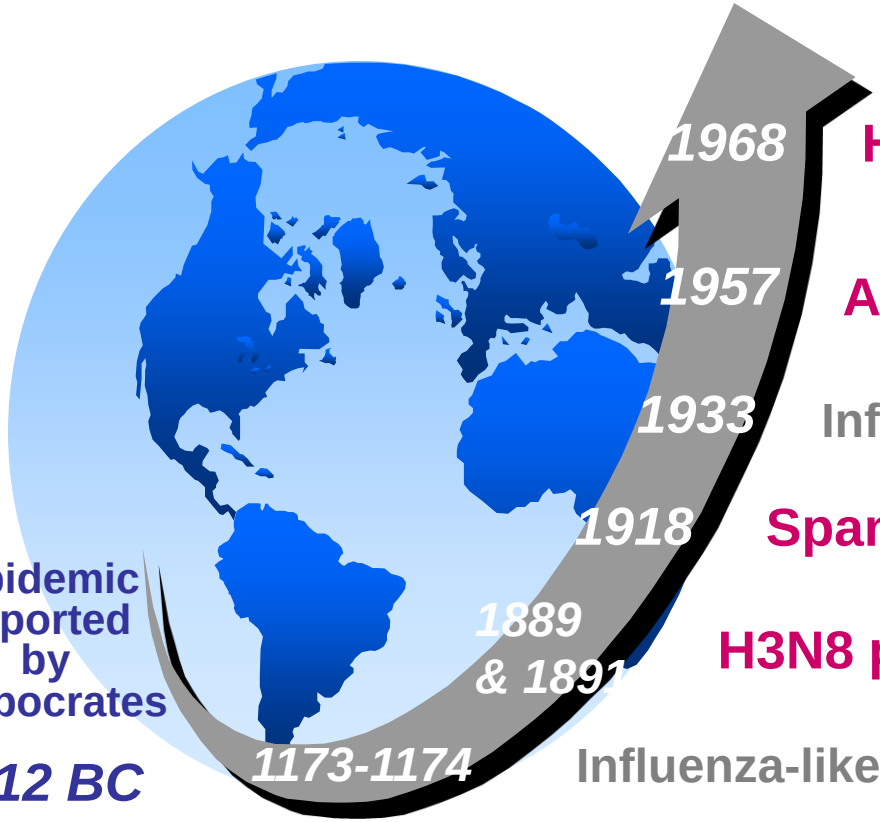
An exceptional epidemiological event:

- **Rapid worldwide circulation of a highly contagious virus**
- **New subtype of an influenza type A virus against which humans have little or no immunological protection**
- **Higher morbidity and mortality than seen with classical annual influenza**

Previous pandemics affected 25–50% of the world population over a 13–23 month period

Young, healthy adults are affected by severe forms of the disease

Influenza pandemics in history



Epidemic reported by Hippocrates

412 BC

1173-1174 Influenza-like epidemics first reported

1889 & 1891 **H3N8 pandemic**

1918 **Spanish flu H1N1**

1933 **Influenza virus isolated for the first time**

1957 **Asian flu H2N2**

1968 **Hong Kong flu H3N2**

Potter CW. A history of influenza. J Appl Microbiol 2001; 91(4):572-579.

Spanish influenza (A/H1N1)
1918 - 1919

1 billion people affected
(25-30% of the world population)

3 epidemic waves:

- **March and September 1918**
- **February 1919**

Exceptionally virulent strain

40-50 Million deaths:

- **> 200 000 in France**
- **500 000 in the USA**
- **1.5-2 Million in Africa**
- **7-10 Million in India**

Asian influenza (A/H2N2) 1957 - 1958

- 2 waves:
  - Children
  - Elderly persons
- 1-2 million deaths worldwide
- Improved surveillance and warning compared to 1918-19 (WHO)
- Vaccines and antibiotics available
- Milder pandemic

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Hong Kong influenza (A/H3N2) 1968 -1969

- Same Asian origin as 1957-58 pandemic
- Milder pandemic (possible cross-protection provided by exposure to the 1957 H2N2 strain)
- 0.8-1 Million deaths worldwide

Influenza Pandemic - Definition

3 conditions for a pandemic

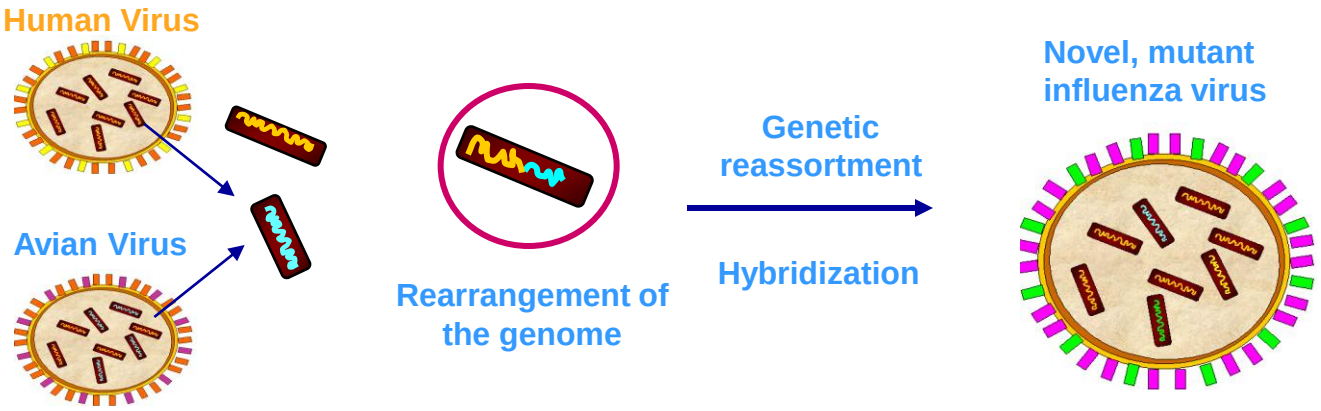
- Emergence of a new influenza A virus with a different HA from those of recently circulating strains
- Absence of immunity in the population against the new strain
- New virus with high virulence and rapid person to person transmission

Mechanisms of emergence of novel human viruses

Adaptive mutation (e.g., Spanish flu)

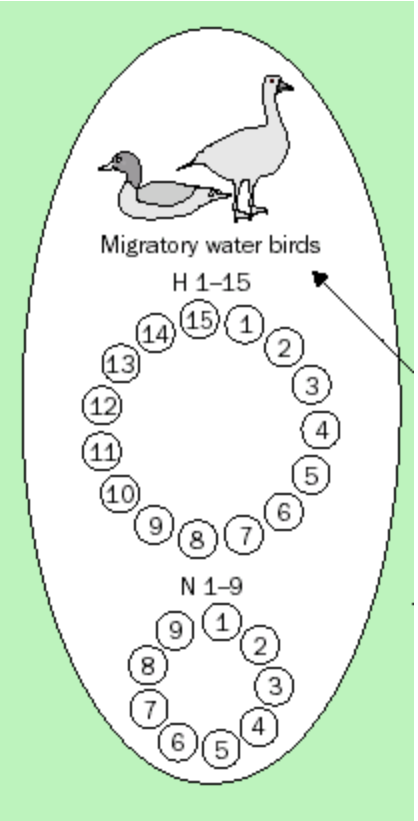
The virus becomes fully adapted to humans through serial genetic modifications during successive infection in humans and other mammals

Gene reassortment from 2 viruses co-infecting a host (e.g., Asian flu)



Strain re-emergence (e.g., Asian flu: H2N2)

Wild birds are the influenza A viral reservoir



Nicholson KG, et al.
Lancet 2003; 362: 1733.

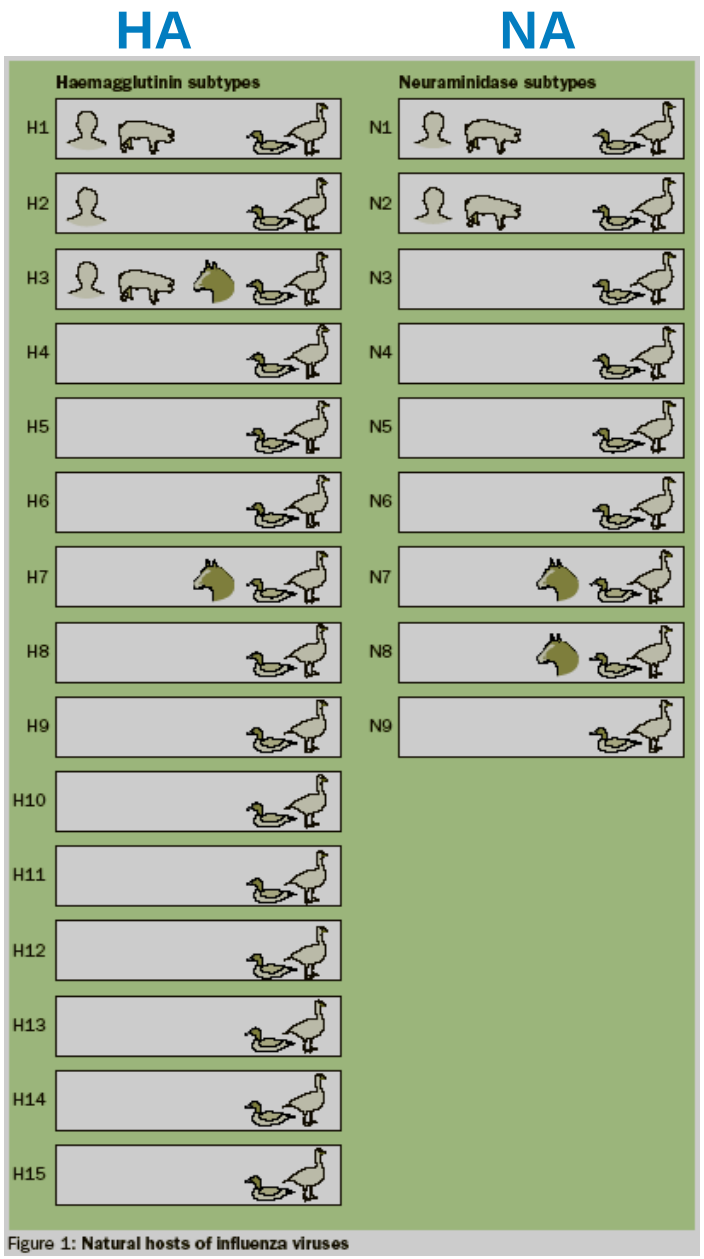


Figure 1: **Natural hosts of influenza viruses**

Influenza's main other natural hosts:
Poultry,
Horses,
Swines,
Humans

Fouchier RA, Osterhaus AD, Brown IH.
Animal influenza virus surveillance.
Vaccine 2003; 21(16):1754-1757

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Cumulative Number of Confirmed Human Cases of Avian Influenza A/(H5N1) Reported to WHO

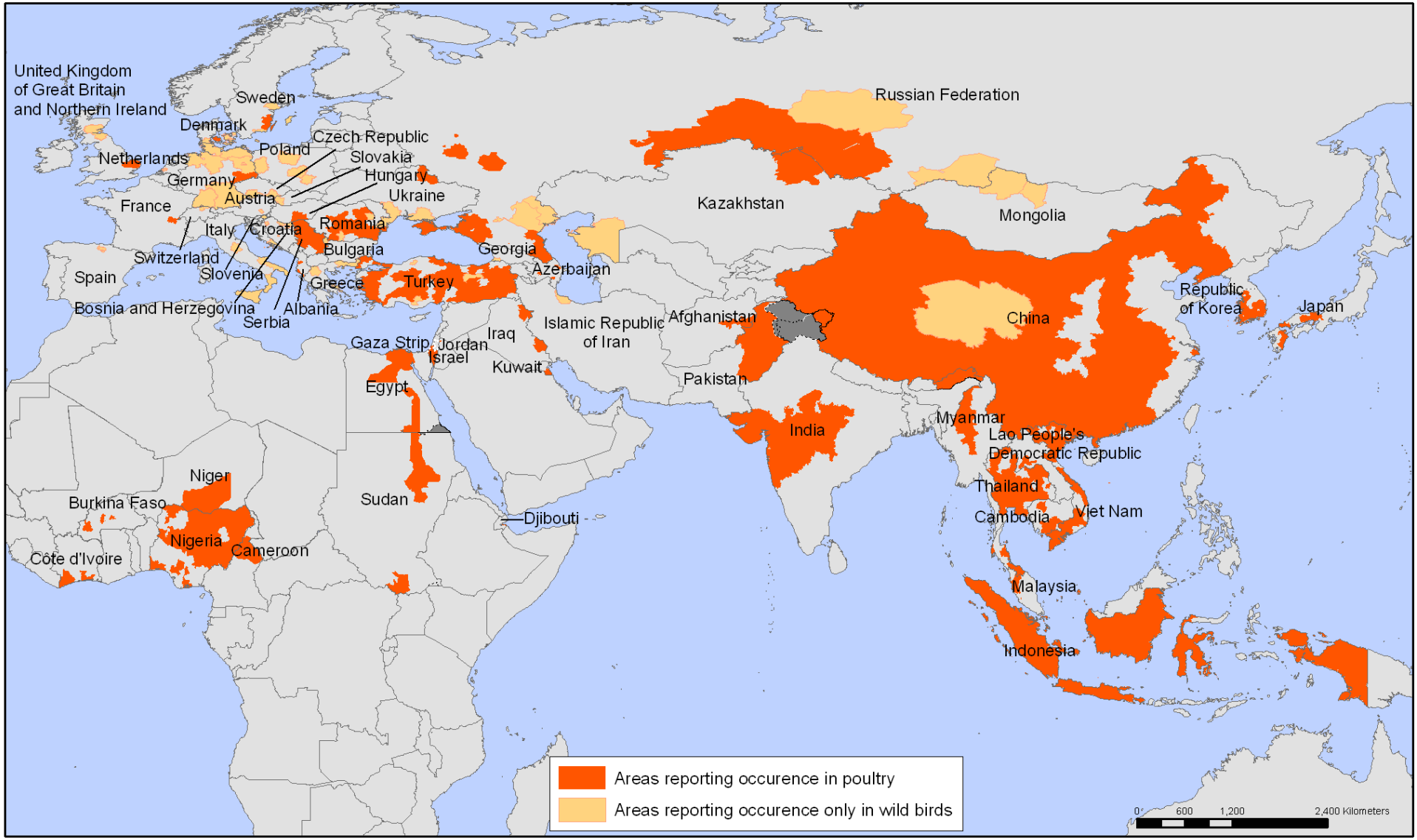
27 February 2007

Country	2003		2004		2005		2006		2007		Total	
	cases	deaths	cases	deaths	cases	deaths	cases	deaths	cases	deaths	cases	deaths
Azerbaijan	0	0	0	0	0	0	8	5	0	0	8	5
Cambodia	0	0	0	0	4	4	2	2	0	0	6	6
China	1	1	0	0	8	5	13	8	0	0	22	14
Djibouti	0	0	0	0	0	0	1	0	0	0	1	0
Egypt	0	0	0	0	0	0	18	10	4	3	22	13
Indonesia	0	0	0	0	19	12	56	46	6	5	81	63
Iraq	0	0	0	0	0	0	3	2	0	0	3	2
Lao People's Democratic Republic	0	0	0	0	0	0	0	0	2	1	2	1
Nigeria	0	0	0	0	0	0	0	0	1	1	1	1
Thailand	0	0	17	12	5	2	3	3	0	0	25	17
Turkey	0	0	0	0	0	0	12	4	0	0	12	4
Viet Nam	3	3	29	20	61	19	0	0	0	0	93	42
Total	4	4	46	32	97	42	116	80	12	9	276	168

Total number of cases includes number of deaths.
WHO reports only laboratory-confirmed cases.
All dates refer to onset of illness.

Areas reporting confirmed occurrence of H5N1 avian influenza in poultry and wild birds since 2003

Status as of 27 February 2007
Latest available update



The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted lines on maps represent approximate border lines for which there may not yet be full agreement.

Data Source: World Organisation for Animal Health (OIE) and national governments
Map Production: Public Health Mapping and GIS
Communicable Diseases (CDS) World Health Organization

Avian influenza epidemics caused by highly pathogenic virus (HPV) H5N1

1959: first epidemics documented in chickens

1997 in Hong Kong

- **1.5 Million chickens culled**
- **18 human cases**
- **6 deaths**

Since December 2003

- **The H5N1 HPV progressively spread**
  - From Thailand, Vietnam and Cambodia, to Laos, South Korea, China, Indonesia, Malaysia, and in 2005 to Mongolia and Kazakhs…etc
- **>140 Million chickens culled**
- **To date (end feb 2007): 276 human cases, including 168 deaths**

Current status of avian H5N1 epidemic

The epidemic is now endemic in the chickens of several Asian countries

Highly Pathogenic Avian Influenza Virus H5N1 has been also isolated from certain species of migrating birds

Ducks can carry the virus,
but most of them do not develop the disease

In addition to humans,
the virus has infected other mammals (felines, ferrets, pigs, New Zealand white rabbit, cynovolgus macchaque…etc)

Pekin Breeder Ducks

Necessary conditions for the emergence of a pandemic influenza virus

I. Emergence of a influenza A virus against which humans have little or no protective immunity

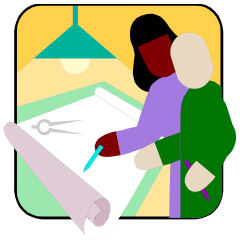
II. The new virus is able to infect and grow in humans, causing severe disease (virulence) ➔ **From December 2003 to Feb 2007, 276 persons were infected (168 deaths) in 12 countries**

III. The new virus is easily and quickly spread from human to human, causing a continuous chain of infection (contagiousness) ➔ **to date, human-to-human transmission is not confirmed with this virus**

World pandemic preparedness

Influenza Pandemic
Why do we need planning?

- It is impossible to predict when the next pandemic will occur
- WHO Weekly Epidemiological Record, November 2002: „inevitable shortage of vaccines and antivirals“
- Worldwide production of influenza vaccines is currently able to cover less than 5% of the world s population.
- In case of a pandemic:
  - severe pressure on health services,
  - social disruption,
  - interruption of commerce, economic losses, etc.



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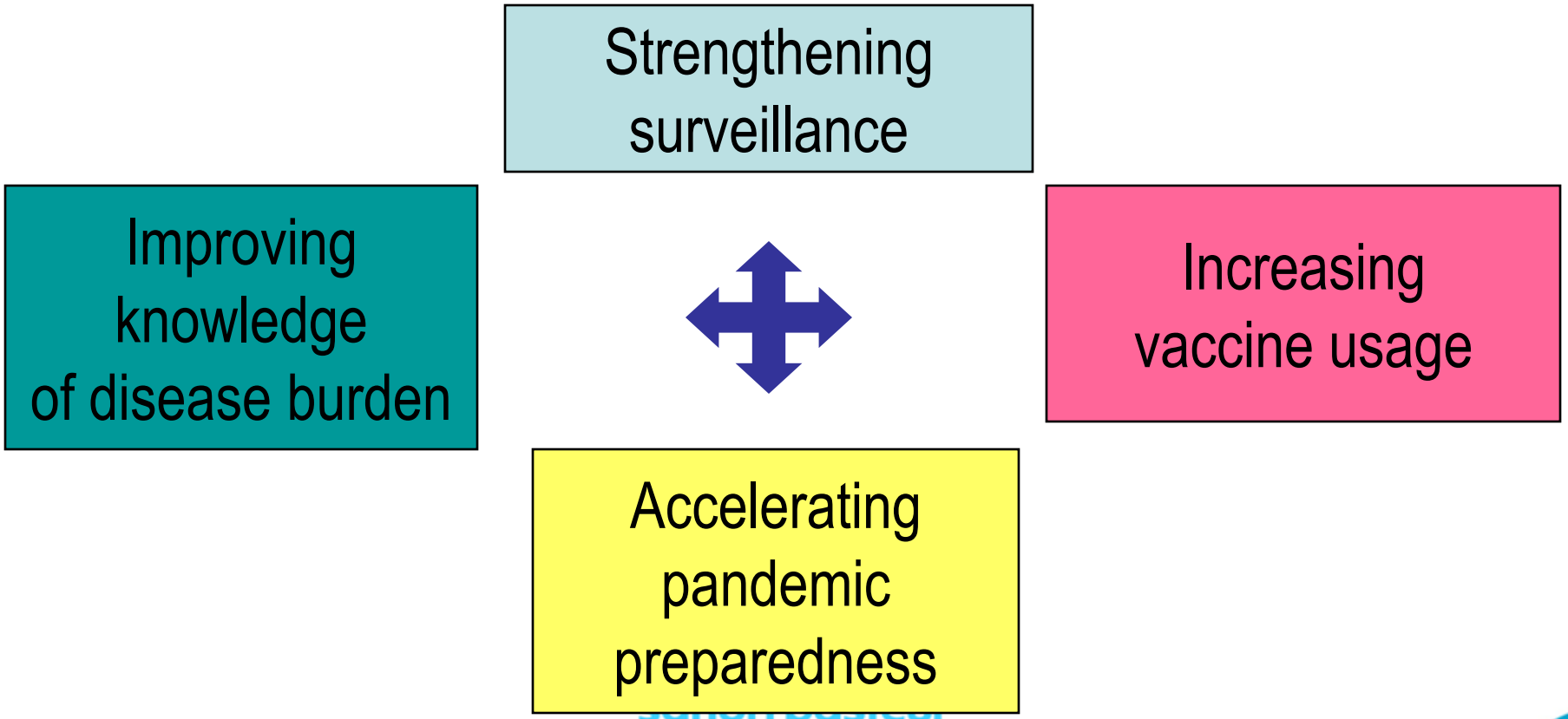
Preparedness plans of WHO, governments and private sector follows the WHO phases

WHO Phases	
Interpandemic period	
Phase 1	No new flu virus circulating in humans
Phase 2	No new flu virus circulating in humans, but an animal virus poses a substantial risk of human disease.
Pandemic alert period (pre-pandemic)	
Phase 3	Human infection with a new virus (no person-to-person transmission, or rare and isolated cases connected to close contact)
Phase 4	Clusters of limited and localized person-to-person transmission (virus incompletely adapted to humans)
Phase 5	Expansion of clusters, still geographically localized (the virus is adapting to humans)
Pandemic period	
Phase 6	Significant person-to-person transmission in the population, with rapid geographic expansion

WHO Global Agenda on Influenza Surveillance and Control

17 priority activities organized around 4 main objectives



Priority groups for vaccination

Each country will need to define its priority groups

- **Essential service providers**
  incl. health care personnel, firemen, police, persons involved in water, gas and electricity distribution, etc.
- **Groups at high risk of death and severe complications**
- **Persons without risk factors for complications**
  Healthy adults and children

„The final choice is a political one“ (Chippaux, 1994)

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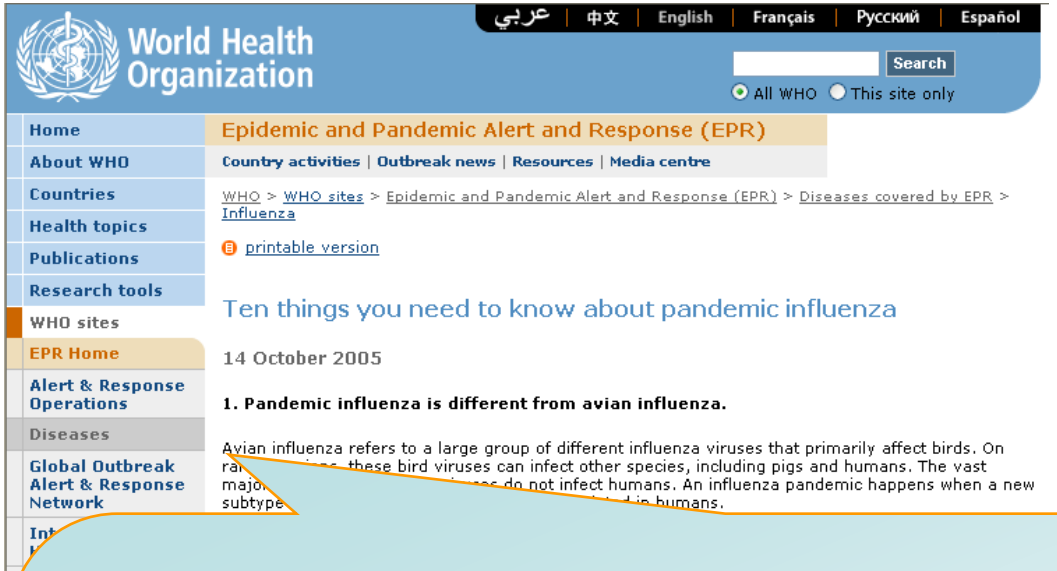
Pandemic preparedness and use of influenza vaccines in Interpandemic periods

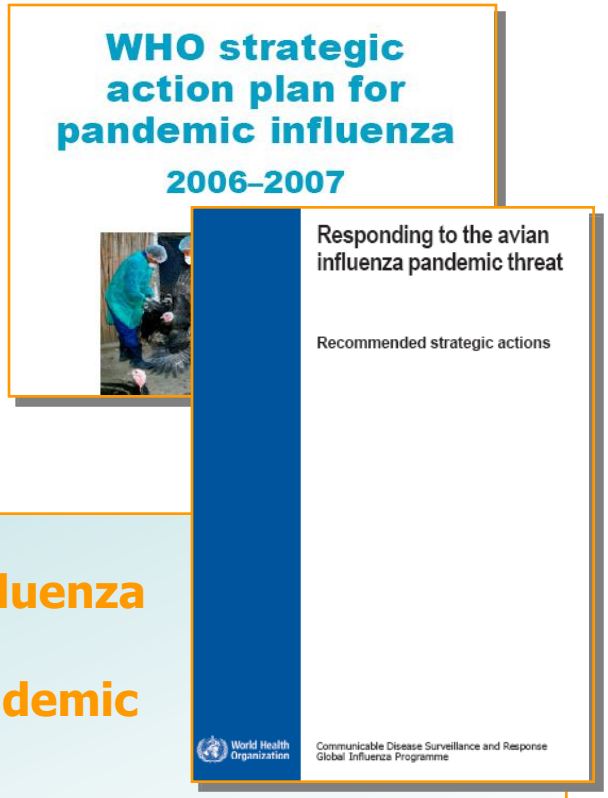
- **Pandemic threat is a major driver for Interpandemic coverage extension**
  - **To increase production capacities**
  - **To avoid genetic reassortment**

- Resolution of the World Health Assembly, May 2003

„Better use of influenza vaccines for seasonal epidemics will help to ensure that manufacturing capacity meets demand in a future pandemic, as well as preventing numerous deaths“

Preparedness activities are in line with the WHO warnings and preparedness guidelines





1. Pandemic influenza is different from avian influenza
2. Influenza pandemics are recurring events
3. The world may be on the brink of another pandemic
4. All countries will be affected
5. Widespread illness will occur
6. Medical supplies will be inadequate
7. Large numbers of deaths will occur
8. Economic and social disruption will be great
9. Every country must be prepared
10. WHO will alert the world when the pandemic threat increases

Thank you !